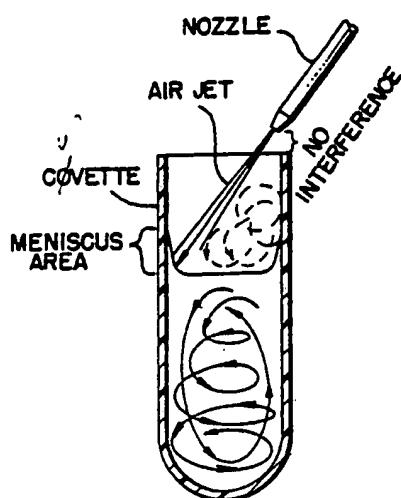




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(54) Title: CLINICAL ANALYSIS SYSTEMS AND METHODS



(57) Abstract

A mixing technique particularly for the clinical analysis of liquid biological samples. The sample is placed in a cuvette (24) along with a reagent and diluent. For mixing the sample with the reagent to facilitate reaction therewith, an air jet is directed against the liquid surface formed in the cuvette (24) adjacent the junction of the liquid surface with the wall of the cuvette (24) by an air-jet mixing apparatus (15) to create a vortex to produce thorough mixing of the contents of the cuvette (24).

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CLINICAL ANALYSIS SYSTEMS AND METHODSBACKGROUND OF THE INVENTION

5 This invention relates generally to the mixing of materials and to the analysis of the results of such mixing. In particular, the invention relates to methods of and systems for the analysis of liquid biological samples. It also relates to methods of and 10 apparatus for mixing materials which are particularly suitable for mixing such a sample with a reagent to produce a reaction for analysis. The present invention is particularly useful in automated chemistry analyzers for determining the presence and levels of one or more 15 selected constituents in relatively small biological liquid samples.

Numerous automated clinical analyzers are known and widely used in hospital clinical laboratories. An example of such an analyzer is the 20 multi-channel type analyzer.

A multi-channel analyzer is one in which a series of different tests are performed simultaneously by the analyzer, and in parallel with one another. Such an analyzer can be best visualized as a series of 25 batch analyzers operating in parallel wherein each channel performs a single analysis test. The multi-channel type analyzer generally utilizes a liquid reagent to react with the particular constituent being tested in the sample and a photo-optical system to read the optical absorbence of the sample which corresponds 30 to the level of the constituent in the sample.

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Although this type of automated analyzers has received wide acceptance in the clinical laboratory certain drawbacks are associated with its use. For example, although the multi-channel type analyzer is 5 reliable due to its simplicity, cost effective for large number of samples and has a relatively high test throughput rate, it is limited in the sense that it can only be effectively utilized to perform a single constituent analysis at a time on a relatively large 10 number of samples. In addition, such analyzers are not capable of performing emergency "stat" tests due to their relatively long and complex set up time and their inherent inability to economically analyze a single test sample.

15 A further significant disadvantage found is that although they can simultaneously perform tests for multiple constituents on the same sample, generally all of these tests must be performed for every sample whether desired or not. This results in a waste of 20 both sample material and the reagents used in the unnecessary tests. Furthermore, due to the fact that multiple discrete and dedicated channels are utilized in such an instrument, there is significant duplication of numerous components which adds to the complexity and 25 expense of the overall instrument.

An automated single track clinical analyzer which avoids the above-described drawbacks is described in commonly owned U.S. Patent Application Serial No. 284,840, filed July 20, 1981 entitled, "Automated 30 Analysis Instrument System", the disclosure of which is hereby incorporated by reference in its entirety herein. By way of contrast to the multi-channel analyzer, the single track analyzer has both discrete

and profile capabilities. The single track analyzer can perform different analytical profiled (i.e., profile analysis) or the same analytical test on a series of different patient samples (i.e., batch analysis). In either mode of the single track analyzer, the cuvettes containing samples are processed serially along a single track within the analyzer. The single track analyzer is capable of performing multiple selected tests on a single specimen and is adapted for handling "stat" testing of emergency samples and routine chemistries. To this end the analyzer is adapted to dispense different permutations of reagent and liquid biological sample into successive relatively small cuvettes advanced therethrough and has multiple analysis stations to which the cuvettes are fed in turn so that examination of the treated samples can be effected at varying time intervals without limiting the throughput of the instrument. These multiple analysis stations permit their positioning at read times that are closely related to theoretical optimal kinetic and endpoint reaction read times. Furthermore, by using a unique photo-optical system, also described in commonly owned U.S. Patent Application Serial No. 284,841, filed July 20, 1981, entitled "Multichannel Spectrophotometer", the disclosure of which is hereby incorporated by reference in its entirety herein, greater flexibility of analysis at each analysis station is achieved. This is because the photo-optical system employs fiber optic bundles or similar light guides to transmit variable wavelengths of light to each analysis station from a single light source.

The single track analyzer utilizes a disposable cuvette belt formed from thin plastic film

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and defining a series of discrete reaction compartments (cuvettes) which are transported in line ahead through the instrument. The cuvettes are relatively small; they are generally for example capable of holding a 5 final reaction volume of approximately 300 microliters. The patent sample in the cuvette is approximately 2020 microliters. Such a cuvette belt is described in commonly owned U.S. Patent Application Serial No. 284,842, filed July 20, 1981 entitled, "Cuvette System 10 For Automated Chemical Analyzers", the disclosure of which is incorporated in its entirety by reference herein. Such a belt provides handling flexibility and avoids the cross-contamination associated with flow-through cuvettes as well as avoiding the washing 15 required of reusable cuvettes.

The earlier clinical analyzers discussed above employed liquid reagent, and mixing of the reagent with the diluent prior to addition of the biological sample was achieved by shooting a stream of 20 the liquid reagent into the cuvette so as to produce a vortex-type mixing process. A preferred feature of the analyzer disclosed in U.S. Patent Application Serial No. 284,840 is that it is adapted to utilize dry particulate reagents, preferably in tablet form, which 25 are dispensed into the cuvettes from a rotating carousal which can hold a large number of doses. A preferred embodiment of tablet dispenser is described in commonly owned U.S. Patent Application Serial No. 285,022, filed July 20, 1981 entitled, "Tablet 30 Dispensing Device", the disclosure of which is hereby incorporated by reference in its entirety by reference herein. In order to effect dissolution of the dry particulate reagent within the diluent prior to

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addition of the biological sample, the reagent and diluent are mixed by ultrasonic means.

A further advantageous feature of such an automated clinical analyzer is the use of 5 microprocessor control, particularly for the dispensing and analysis station and the loading and transfer assembly for presenting to the analyzer containers having the samples to be tested.

10 A particular embodiment of the automated single track clinical analyzer according to aforesaid U.S. Patent Application Serial No. 284,840 is the subject of the Paramax Analytical System manufactured by American Dade, a division of American Hospital Supply Corporation, of Miami, Florida. "Paramax" is a 15 registered trademark of American Hospital Supply Corporation. In this system, which is under microprocessor control, a cuvette belt is cut into sections, comprising one or several cuvettes, which are fed in turn past a reagent tablet dispenser, a diluent 20 dispenser, an ultrasonic horn for mixing the reagent and diluent, a sample dispenser and eight photo-optical analyzer stations. During their passage through dispensing and analysis, the cuvettes are supported in a water bath kept at a constant temperature and after 25 analysis they pass through a sealing station and into a disposal station.

Reagent tablets are dispensed from a rotary carousel and the biological liquids to be sampled are delivered in tubes to the sample dispenser one at a 30 time by a carousel having priority access positions to allow immediate "stat" sample entry. Codes on the tubes identify the samples and a code-reader alerts the microprocessor to operate the analyzer in accordance

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with the coded information. A further reagent dispenser is arranged between two of the analyzer stations for producing further sample reaction to permit additional analysis.

5

SUMMARY OF THE INVENTION

In the prior clinical analyzers as described above, the reagent and diluent are mixed in the cuvette 10 prior to the addition of the liquid biological sample, either by shooting the reagent into the diluent to form a vortex in the case of a liquid reagent or by ultrasonic mixing in the case of the dry particulate reagent.

15

It has been found in accordance with the invention that improved reliability and controllability of the analysis of the samples is achieved by again mixing the contents of the cuvette after addition of the sample by directing an air jet to an acute angle 20 against the surface of the liquid in the cuvette. Particularly good mixing is obtained in accordance with a feature of the invention where the air jet is directed at the liquid surface adjacent its junction with the wall of the cuvette. The optimum point of 25 contact of the air jet with the liquid surface has been found to be at the meniscus formed at the junction between the liquid surface and the wall of the cuvette.

30

The combination of directing the air jet against the liquid surface adjacent its junction with the wall of the cuvette and directing it at an acute angle to the surface producing a horizontal component has the beneficial effect of creating a vortex which produces a thorough mixing of the contents of the

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cuvette. Thus, a whirling or circular motion is induced in the contents tending to form a cavity of vacuum in the center and to draw the materials at the edge towards the center thus providing an effective 5 mixing action. Particularly where the air jet hits the contents of the cuvette in the meniscus region, the contents tend to be raised up the wall of the cuvette opposite where the air jet hits the contents creating a particularly effective vortex producing very good 10 mixing of the sample with the diluent and reagent. Thus a particulate reagent will become totally suspended within the diluent and the sample optimizing the reaction of the sample therewith.

By controlling the level of liquid in the 15 cuvette and the air jet, splashing of the contents out of the cuvette leading to intercuvette contamination can be avoided. Splashing can, for example, be avoided by controlling the pressure of the air jet and/or by pulsing the air jet on and off.

20 The air jet may be directed at the liquid surface in the cuvette from a nozzle arranged inside the cuvette, but, in a preferred embodiment, the air jet is directed into the cuvette from outside the cuvette. Thus, a cuvette partially filled with the 25 diluent, reagent and sample is disposed beneath an inclined nozzle and an air jet is directed at the liquid surface in the cuvette adjacent its junction with the wall of the cuvette from the nozzle.

30 In an automated system, the cuvette is partially filled to a predetermined liquid level and then advanced into alignment stationarily beneath a fixed nozzle so that the latter is aimed at the junction of liquid surface and cuvette wall. The angle

of the air jet nozzle should ideally be as far as possible from the vertical providing maximum horizontal components of the air jet upon the liquid. The angle is determined by the diameter of the cuvette, the 5 liquid level in the cuvette, which is itself controlled by the requirement to avoid splashing of the contents out of the cuvette, and the position of the nozzle over the mouth of the cuvette.

To obtain the optimum angle, the nozzle 10 should be arranged diametrically opposite the point at which the air jet hits the liquid surface. Thus, in a preferred embodiment, the liquid level in the cuvette is suitable about 15 mm to about 25 mm below the mouth of the cuvette with the nozzle arranged to direct the 15 air jet at an angle of between about 75 degrees and about 80 degrees to the liquid surface (horizontal), the cuvette being arranged vertically. When the cuvette has an elongated cross-section, the air jet is suitably aligned with the longer cross-sectional 20 dimension.

The cuvette may be tilted towards the nozzle to permit the angle of the nozzle to be more horizontal.

It has been found that activation of the air 25 jet for a period of between about 3.5 seconds, and about 4.5 seconds, preferably about 4 seconds, is usually sufficient to provide good mixing of the diluent, reagent and sample.

It will be understood from the foregoing that 30 the invention has various advantages. It permits thorough mixing of the reagent, diluent and sample which enhances reliability and controllability of the test(s) of the sample. The mixing process occurs in a

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very fast timeframe. Intercuvette contamination is avoided by controlling the mixing action so that splashing of material out of the cuvette is prevented. There is no physical contact between the nozzle and the 5 contents of the cuvette and by having the nozzle arranged outside the cuvette, contamination of the nozzle is avoided and there is no need to move any component into the cuvette to effect the mixing, thus maximizing throughput in an automated process.

10 While it is preferred, particularly in an automated process, that the air-jet nozzle direct air into the cuvette from outside the cuvette, it is within the spirit and scope of this invention to direct the air jet from inside the cuvette and aimed at the liquid 15 surface from a position above the liquid surface. While requiring insertion and removal of the nozzle into and out of the cuvette (either by lowering and raising the nozzle or by raising and lowering the cuvette) this does have the advantage that the nozzle 20 can be angled more closely to the horizontal without spilling of the contents. Thus, the nozzle may be inclined at an angle of between about 0 degrees to about 90 degrees to the horizontal, with the preferred embodiment of between about 8 and 15 degrees. 25 Depending upon the height of the nozzle above the liquid surface, it may become contaminated by the liquid as it is agitated in which case it should be cleaned with diluent between mixing operations. It will be noted that in this embodiment as well as in 30 that described above, the nozzle is arranged above the liquid surface and is therefore non-invasive of the liquid.

An automated analyzer system according to this

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invention may incorporate any or all of the features described in aforesaid U.S. Patent Application Serial No. 284,840. Thus, in one preferred form of the invention, a dry particulate reagent, preferably in tablet form, is dispensed into the cuvette together with a diluent and subject to ultrasonic mixing to effect dissolution of the reagent and dispersal in the diluent. A second, liquid reagent may be added at the same time as the diluent. The system has multiple analysis stations, having a photo-optical system as described in aforesaid U.S. Patent Application Serial No. 284,841 to which the cuvettes are fed in turn. A further reagent dispenser is arranged between two of the analysis stations and a further mixing station, according to the invention, is arranged immediately following this dispenser which acts on each cuvette into which further reagent (preferably liquid) has been dispensed by directing an air jet against the liquid surface adjacent its junction with the cuvette wall to enhance further reaction of the sample.

While the unique air-jet mixing system of this invention has particular application to the mixing of biological samples in clinical analyzers as described above, it also has general application to the mixing of liquids with one or more other liquids or solids.

DESCRIPTION OF THE DRAWINGS

Other features and advantages of the present invention will become apparent from the following description taken in conjunction with the accompanying drawings wherein:

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Figure 1 is a schematic plan view of an automated clinical analyzer according to the present invention;

5 Figure 2 is a partial perspective view of the automated clinical analyzer shown in Figure 1;

Figure 3 is a perspective view of a preferred photo-optical analysis system used in the clinical analyzer of Figure 1;

10 Figure 4 is a perspective view of a cuvette belt for use in the clinical analyzer of Figure 1;

Figure 5 is a plan view of the cuvette belt shown in Figure 4;

15 Figure 6 is a schematic side elevation of a mixing apparatus according to the invention of the clinical analyzer of Figure 1;

Figure 7 is an enlarged view of Figure 6 showing the relationship of the mixing apparatus and the cuvette;

20 Figure 8 is a plan view further illustrating the relation of the mixing apparatus and the cuvette;

Figure 9 is a side view of a modified form of cuvette;

25 Figure 10 is a schematic side elevation like that of Figure 7 showing the mixing action produced when the apparatus is in use; and

Figure 11 is a schematic side elevation of a second embodiment of mixing apparatus according to the invention suitable for use in the clinical analyzer of Figure 1.

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DESCRIPTION OF THE PREFERRED EMBODIMENTS

Figure 1 and 2 illustrate an automated clinical analyzer 10 generally as described in the aforesaid U.S. Patent Application No. 284,840 modified by the inclusion of mixing means in accordance with the present invention. More particularly, the analyzer is a modified Paramax Analytical System as manufactured by American Hospital Supply Corporation. The analyzer 10 is adapted for the testing of constituents in biological fluids, such as blood samples.

The analyzer comprises a series of processing stations past which strips of disposable reaction cuvettes are indexed or advanced. The cuvettes 24 are supplied from a supply reel 20 as a continuous cuvette belt 22 and are indexed through the analyzer by tractor conveyor 30 which engages a row of index holes in the cuvette belt. The cuvettes are indexed in turn past the following stations: a belt cutter 28 for dividing the belt into sections; a tabletted reagent dispenser 40; a diluent and liquid reagent dispenser 50; a ultrasonic mixing horn 14; a sample dispenser 80 for dispensing biological samples delivered by a transfer carousel 64; an air-jet mixing apparatus 15 according to the invention for mixing the sample with the reagent and diluent in the cuvettes; eight photometric read stations 90; a further reagent dispenser 54; a further air-jet mixing apparatus 15a according to the invention for mixing the sample and the further reagent; a cuvette sealer 16 and a cuvette collection station 18. During their passage through the analyzer, the cuvettes are carried in a water bath 12 maintained at a constant temperature. These stations and their functions will

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now be described in detail.

The disposable cuvettes 24 are conveniently packaged in reels of as many as 2100 cuvettes. The belt 22 defined entirely separate reaction vessels 5 designed to eliminate cross-contamination of reaction mixtures. The cuvette belt 22 is preferably constructed and made in the manner more fully described in aforesaid U.S. Patent Application Serial No. 284,842 as will now be described briefly with particular 10 reference to Figures 4 and 5.

The belt 22 comprises two strips 111, 112 of transparent plastics material which are moulded and sealed together to form a series of discrete, side-by-side parallel compartments (cuvettes) 24 separated by webs 115. The compartments are closed at one end and have an open mouth 117 at the other end so as to receive and retain fluid therein. For example, the cuvettes can be in the order of size so as to be capable of holding about 500 microliters of fluid. The 15 compartments or vessels 24 are substantially rectangular in cross-section, being elongated along the length of the belt. They have generally parallel side faces 124 which define optical windows providing an optical path of precise length through each cuvette for 20 accurate examination of the samples at the read stations 90. The flat web material 115 between the vessels 24 includes a transport strip portion extending alongside the closed ends thereof which is formed with indexing perforations or hole 26. These perforations 25 are engaged by the tractor transport 30 of the analyzer 30 for conveying the cuvettes therethrough and maintaining a precise alignment of the optical paths 30 through the cuvettes with the photo-optical examining

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system at the analysis stations 90.

The cuvette strips 111, 112 are conveniently made by forming a series of shallow, laterally extending depressions along a web of plastic material 5 which is twice the width of a strip 111 or 112 and then cutting along the center-line of the web to form two of the strips 111, 112. The web may be cut and the two strips which are obtained then joined together to form one belt 22 or two webs may first be joined together 10 and then cut along the center-line to form two belts 22. It has been found that by forming the webs using cold molding techniques, optical degradation of the web material is avoided and if the portions of the web which form the side faces 124 of the vessels 24 are 15 restrained during forming to prevent stretching thereof, the optical windows of the resulting vessels are maintained stress-free and with a uniform thickness. Webs of copolyester, such as KODAR brand thermoplastic polyester resin material made by Eastman 20 Kodak Co., or vinyl plastic sheet stock about 0.003 to 0.010 inch thick have been found to provide satisfactory results. In order to facilitate fabrication and assembly of the cuvette belt, the strips may be a laminate having a layer of an easily 25 sealable and biologically inert material such as SURLYN brand inomer resin material manufactured by E.I. DuPont de Nemours & Co., Inc.

While the cuvettes shown in Figures 4 and 5 have a generally uniform cross-section, in a preferred 30 cuvette belt for use with the present invention, as shown in Figure 9, the mouths 117 are enlarged in the direction along the belt as explained more fully hereinafter.

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The transport 30 comprises a single continuous guide and support track extending through the analyzer having a main tractor belt 32 which engages the indexing holes 26 in the cuvette belt 22 and advances the cuvettes through the instrument at a predetermined rate of advance. A short loading belt 34 threads the cuvette belt 22 into engagement with the main tractor belt 32. The transport 30 advances or indexes the cuvettes through the analyzer 10 in steps corresponding to the spacing between cuvettes (the pitch of the belt) with the cuvettes being stopped and held stationary for a dwell period between each advance. Each step may suitably correspond to a time interval of 5 seconds with a 4 second dwell time between each indexing advance of the cuvettes.

The reagent tablet dispenser carousel 42 comprises a circular array of tabletted reagent dispensers 40 and can be rotated to bring the correct solid reagent dispenser to solid reagent dispensing point "SRD" to drop a single reagent tablet 44 into a cuvette 24. As illustrated, the carousel 42 accommodates thirty-two reagent tablet dispensers 40. It is rotated under microprocessor control to bring the correct tablet dispenser to the dispensing point for each cuvette. The dispensers 40 are detachable and can be loaded randomly. An automatic flagging system indicates when a dispenser is low in tablets.

The diluent and/or liquid reagent dispenser 50 is located adjacent to carousel 42 for adding sufficient diluent 52 for reagent tablet 44 dissolution and/or for dispensing a liquid reagent into the reaction vessel (cuvette) 24 at point "LDD".

The ultrasonic horn 14 acts on the cuvette

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contents for a sufficient length of time; for example, 45 seconds, to totally dissolve the reagent tablets.

A sample loading and transfer carousel assembly 60 is located downstream of the reagent and diluent dispensers. This carousel assembly comprises a loading carousel 62 into which patient samples 70 are randomly loaded; a transfer carousel 64 which accepts the patient samples 70 from loading carousel 62, identifies the patient sample by means of a bar code reader 66 which reads a bar code label 72 placed on the patient sample container and continuously feeds the patient samples into the system; and finally, an unloading carousel 68 receives the patient samples 70 after testing and stores them in an organized manner in the event that they must later be located and retrieved.

The loading carousel 62 permits continuous random loading of up to 96 patient samples. The transfer carousel 64 continuously feeds patient samples into the system for maximum throughput. Standard collection tubes or micro sample tubes may be accommodated thus allowing utilization of the same containers in which the sample was collected; for example, in the case of blood samples, the 'Vacutainer' tube which is commonly used to draw the serum specimen.

Sampler 80 for dispensing samples into the cuvettes 24 at point "SD" is located adjacent to transfer carousel 64. This sampler is designed to aspirate about 2 to 20 microliters of patient sample 70 from its container in the transfer carousel and dispense it into a cuvette 24 during the four second dwell period while the cuvette is aligned with the sampler.

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The air-jet mixing apparatus 15 (and 15a) according to the invention direct an air jet at an acute angle against the liquid surface in the cuvette adjacent its junction with the cuvette wall to create a vortex thus producing a thorough mixing of the sample with the reagent and diluent. In a preferred embodiment, the apparatus has a fixed, inclined nozzle 150 and the cuvettes 24 are aligned in position beneath the nozzle and the air jet is switched on only during the dwell period when the cuvette is stationary. In order to ensure that the air jet correctly strikes the liquid surface, the liquid level is closely controlled. The structure and operation of preferred embodiments of the air jet mixing apparatus 15 and 15a are described in detail hereinafter.

Eight photometric analysis stations 90 are located at points "SA1" through "SA8" along the cuvette track 30. These analysis stations are connected by individual optical guides 92 and 94 to photo-optical system 100. The station "SA1" is arranged following the ultrasonic horn 14 for verifying proper reagent dispensing and dissolution. This system is illustrated in Figure 3.

The photo-optical system comprises a single light source 101 for generating selected wavelengths of light. The output of light source 101 is focused by fixed focusing lens 102 onto the multiple wavelength selective filters disposed about the circumference of rotary source filter wheel 103. The rotation of source filter wheel 103 is regulated by the instrument control microprocessor through double shafted motor 104. The output from source filter wheel 103 is sequentially transmitted through separate light guides 92 to each of

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the analysis stations.

At the analysis stations, the filtered light energy is passed through the reaction compartment 24 containing the mixture to be analyzed. The output of 5 the analysis stations is then passed back to the photo-optical system 100 via separate light guides 94. At this point, a second filter wheel 107, which preferably is identical to and synchronized with source filter wheel 103, intercepts the outputs of light guides 94 10 before this output is directed to a separate photodetector tube 109 for each analysis station. A reflector 108 may be utilized to focus the output of filter wheel 107 on photodetector tubes 109. In the 15 representation of Figure 3, only one set of light guides 92, 94 and one photodetector tube 109 is shown for simplicity, although it is to be understood that eight of these elements (one for each analysis station) are required.

20 The outputs of photodetector tubes 109 are monitored by the control microprocessor and appropriate wavelength output values for each analysis reaction at each analysis station is stored by the microprocessor. When the reaction is completed, the microprocessor will 25 utilize this stored information to calculate the concentration of the selected sample constituent and provide this result to the instrument operator.

As can be seen from Figure 3, each filter wheel has seven different wavelength selective filters 30 105 disposed about its circumference. In addition, an opaque blank 106 is located thereon in order to establish the residual "dark current" level of the electronics. Hence, great flexibility is provided by permitting any one or combination of the seven

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wavelengths to be read at any analysis station for any sample during the four second analysis period. In that filter wheels 103, 107 are rotated at thirty revolutions per second in the preferred embodiment, 5 thirty readings at a particular wavelength may be made each second which can then be averaged to provide a highly accurate final value by the microprocessor.

The second reagent dispenser 54 permits further reaction of the sample to be obtained following 10 initial testing and is shown arranged between analysis stations "SA4" and "SA5". It could be located between any of the analysis stations "SA2" to "SA8". This capacity for optional reagent additions or triggered reaction capability gives added analytical versatility 15 for multiple reagent test situations.

The further air-jet mixing apparatus 15a according to the invention provides for thorough remixing of the cuvette contents following addition of further reagent at station 54.

20 The cuvette sealer 16 seals the tops of the tested cuvettes for convenient clean disposal of completed samples at the cuvette disposal location where they are neatly collected into a lined disposal bin.

25 The microprocessor control system of the clinical analyzer, which suitably has a 280 processing unit, controls all the operating units thereof in accordance with sample and test information inputted at a suitable operator interface keyboard. In accordance 30 with the desired test results, quantities of a single sample may be dispensed into one or more cuvettes either alone or in combination with any one or more of the solid and liquid reagents and diluent and examined

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at any one or more of the analysis stations 90. Test results are displayed on a screen and can be printed out.

Turning now to the detailed operation of the instrument system, a phlebotomist draws a patient blood sample 70 which is positively identified by a bar code label 72 placed on the container in which the sample is drawn. After centrifuging the sample to separate the sera, the sample along with as many others as desired is placed in loading carousel 62 which is then placed into the instrument loading and transfer carousel assembly 60. For emergency stat testing, the patient sample 70 may be loaded directly into one of the empty sample receiving slots 65 of transfer carousel 64, or may be exchanged with a sample container already loaded in transfer carousel 64 prior to bar code reader 66.

The loading carousel is then automatically indexed to a position where the patient sample 70 is transferred into an empty sample receiving slot 65 of transfer carousel 64. The transfer carousel 64 then indexes around to bar code reader 66 which identifies the patient sample. This sample identity is fed to the instrument control microprocessor which correlates this information with the test requisition for this sample that has already been entered into the instrument computer system by the laboratory technician.

The control microprocessor then begins the advance of the cuvette supply reel 20 and belt 22 into cuvette track 30 in response to this sample identification. This cuvette supply advance is accomplished by the loading belt 34 which threads the cuvette belt into main transport belt 32. If bar code reader 66 detects that there are no further samples to

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be tested, the control microprocessor will activate cuvette belt cutter 28 which divides cuvette belt 22 into sections 29 having a number of cuvettes corresponding to the number of analysis reactions to be 5 performed at a given time. This procedure minimizes waste for single tests or stat situations. In addition, the cuvette belt cutter 28 may also be periodically operated during continuous operation of the instrument in order to prevent the length of the 10 cuvette belt (which must be disposed of) from becoming unmanageable.

As it is fed into the instrument, the cuvette belt 22 enters a water bath 12 which will maintain the reagent and sample reaction mixture at a predetermined 15 incubation temperature. This reaction temperature is generally either 30 degrees C or 37 degrees C.

For the sake of simplicity, it should also be noted that in Figure 1 each circular cuvette position point 25 along cuvette track 30 represents a 5 second 20 period. In other words, every 5 seconds the control microprocessor will step a particular cuvette reaction compartment 24 to the next circular position along the cuvette track 30.

During the time that the transfer carousel 64 25 is indexing the sample 70 between the bar code reader 66 and its position where sampler 80 aspirates a portion thereof, an appropriate reagent is added at either point "SRD" or "LDD" to the reaction compartment that is timed by the control microprocessor to receive 30 the sample. The microprocessor causes the proper reagent to be dispensed from one of the thirty-two different tabletted reagent dispensers 40 that can be accommodated by dispenser carousel 42, or the multiple

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liquid reagents that can be accommodated by diluent/liquid reagent dispenser 50, in response to the patient sample identification by bar code reader 66.

If a tabletted reagent is dispensed,
5 sufficient diluent for tablet dissolution is added thereto at point "LDD" and an ultrasonic horn 14 is utilized to provide 45 seconds of high energy ultrasound to completely break up and dissolve the reagent tablet. In the preferred embodiment, this reagent
10 mixture has a volume of 200 microliters.

After this reconstitution of the reagent in the predetermined amount of diluent, the reaction compartment is passed to a reagent quality control analysis station at point "SA1". Here, each reagent
15 mixture is photometrically analyzed to verify proper reagent dispensing and dissolution. Furthermore, the microprocessor can also utilize this reading to adjust for any minor variation in reagent amount and resulting concentration that may exist from tablet to tablet.

20 Next, the reaction compartment 24 is transported to point "SD" where sample 80 will dispense the appropriate patient sample into the reaction compartment 24. As noted above, the main transport belt 32 of cuvette track 30 is carefully synchronized
25 with the reagent dispensers and the sample to insure that the proper reaction mixture is obtained as ordered by the control microprocessor. Since sampler 80 is the only non-discrete element of the analysis system, its probe is flushed with additional diluent to prevent
30 contamination and carry-over between samples. In the preferred embodiment, the final reaction volume is 300 microliters. Following addition of the sample, the contents of the cuvette are thoroughly mixed at air-jet

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mixing station 15 which is described in detail hereinbelow.

5 The next analysis station is the sample blanking station located at point "SA2". It has been found desirable to dispense an amount of each patient sample into a reaction compartment without a reagent being added to obtain a sample blank. This sample blank value may be obtained at this analysis station or any of the following six analysis stations as required.

10 The second reagent dispenser 54 is located further down the cuvette track 30 for multiple or triggered reaction capability. For example, such a reagent dispenser would be useful in conducting CKMB constituent analysis. The further air-jet mixing 15 station 15a provides thorough mixing of the cuvette contents following this addition.

20 At the end of the cuvette track 30, the cuvette sealer 16 is located to seal the tops of the cuvette reaction compartments after testing for 25 convenient and sanitary disposal of the samples. After passing through the cuvette sealer 16, the cuvette belt 22 is stripped off of the main transport belt 32 by an unloading belt 36 which removes the tested cuvettes from the water bath 12 and automatically discards them into disposal bin 18.

30 Turning now to Figures 6 to 11, embodiments of mixing apparatus according to the invention suitable for use on the above-described automated clinical analyzer 10 at mixing stations 15 and 15a will now be described. Figure 6 shows an embodiment of mixing apparatus 15 comprising a nozzle 150 arranged above the path of the cuvettes 24 with which the cuvettes are aligned in turn so that the nozzle is directed at an.

-24-

acute angle at the junction between the surface of the liquid in the cuvette and the wall of the cuvette. The nozzle 150 is fixed in position. In order to insure that the air-jet J produced thereby is properly 5 coordinated with the liquid surface in the cuvette so that it strikes the surface at the junction thereof with the cuvette wall, the quantities of reagent, diluent and sample are closely controlled so that the liquid in all the cuvettes is at a constant preset 10 level. (One exception to this is where the sample is dispensed into a cuvette alone for sample blanking and mixing is not required.)

The nozzle 150 is mounted on a frame 151 so that its orifice is just above the tops of the cuvettes 15 with sufficient clearance to avoid interference with the cuvettes as they are advanced. It may, for example, be about 0.7 mm above the tops of the cuvettes. While the nozzle is fixed in position during use the frame 151 may incorporate means for adjusting 20 the angle of the nozzle either manually or automatically during set-up or between runs. A valve 152 is provided for controlling the supply of air to the nozzle 150 from an air supply 153 to which it is connected by an air line 154. Operation of the valve 25 152 is by means of a controller 155 connected to the analyzer's microprocessor.

As explained above, the cuvettes are indexed stepwise through the analyzer along track 30 and each cuvette is positioned stationarily in alignment beneath 30 the orifice of the nozzle 150 during the dwell period between advancing steps. Activation of the air jet J is limited to this dwell period so that the cuvettes are stationary during mixing.

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It has been found that by directing the air jet J at an acute angle at the junction of the liquid surface in the cuvette with the cuvette wall, preferably so that it hits the meniscus at this 5 junction, a vortex is created which produces a thorough mixing of the contents of the cuvette. This mixing is such that even a reagent which is particularly immissible in the diluent becomes totally suspended within the diluent and the reaction between the reagent 10 and the sample is more complete and rapidly achieved. Figure 10 shows a representative pattern of such mixing within the cuvette by the air jet J, however, the exact pattern of mixing taken by the material may be any suitable one. By ensuring that the air jet hits the 15 liquid surface in the meniscus area, it has been found that very good mixing within the material is achieved. During such mixing, it is seen that the materials climb the wall of the cuvette opposite the point where the air jet strikes the liquid surface. This is depicted 20 by the dotted swirling action behind the air jet at the right-hand side of the cuvette in Figure 10. The use of an air jet to mix the contents of the cuvette in the manner described has been found to work surprisingly well considering the relatively small amount of fluid 25 being mixed and the relatively small confines of the cuvette in which the mixing has to take place.

It has been found that arranging the air jet J at an acute angle as possible so that the horizontal components of the air jet are maximized produces the 30 most beneficial results. In the embodiment of Figures 6 to 8, the angle of the air jet is limited by the level of the liquid in the cuvette which is itself limited by the need to avoid the contents splashing out

of the cuvette during mixing. In order to maximize the inclination of the air jet, the nozzle 150 is arranged just above the cuvette diametrically opposite the point at which the air jet strikes the liquid surface.

5 In the embodiment illustrated, the cuvettes are generally rectangular in cross-section with their longer dimension extending along the length of the cuvette belt. In order to maximize the inclination of the air jet, the nozzle 150 is as shown in Figure 8
10 directed along the longer cross-sectional dimension of the cuvette. Another way of maximizing the angle of inclination of the air jet is shown in Figure 9 which illustrates a modified form of cuvette particularly suitable for use with the present invention which has
15 the mouth of the cuvette enlarged in the dimension along the length of the cuvette belt.

 In still one other embodiment, the air jet of the nozzle can be aligned along the longer cross-sectional dimension of the cuvette and coincident with
20 the longer inside surface of the cuvette. In this manner, a larger area of meniscus may be affected by the jet thereby further enhancing the mixing action.

 It has been found that the preferred angle of inclination of the air jet to the liquid surface may
25 vary between about 75 degrees and about 80 degrees with best results at about 75.5 degrees while the distance between the mouth of the cuvette and the liquid level varies between about 15 mm and about 25 mm. This is when the cuvette is arranged vertically.

30 It will be understood that the pressure of the air jet is also a factor which affects mixing and splashing. The actual air jet pressure will vary depending upon the height of the nozzle above the top

of the fluid in the cuvette. In an embodiment disclosed herein, for example, wherein the nozzle is about .030 inches, above the fluid top level, it has been found that an air jet pressure of between about 2 5 psi and about 3 psi is adequate. Such a pressure may be achieved using simple 'air dryer' or 'acquarium' or like type of pump.

In a preferred embodiment in which the cross-sectional dimension of the cuvette along which the air 10 jet is directed is about 5.1 mm, the nozzle is inclined at an angle of degrees to the cuvette and the cuvette contains 300 microliters of materials defining a liquid level which is about 20.6 mm below the mouth of the cuvette while the air jet pressure is about 2.5 psi.

15 While the mixing time of 4 seconds has been found effective for use in the embodiment described above, the time period may vary, for example, between about 3.5 seconds and about 4.5 seconds depending upon the materials to be mixed and the other parameters 20 described above. In this embodiment, the air jet is activated continuously over such time period.

In operation, the cuvettes 24 are advanced in turn into position beneath the nozzle 150 in alignment therewith which is closely controlled by the tractor 25 belt 32. The microprocessor, which has already closely controlled the quantities of materials dispensed into the cuvette to the preset liquid level, directs the air jet at the meniscus at the junction between the liquid surface and the cuvette wall to create a vortex which 30 produces a thorough mixing of the contents of the cuvette. At the end of the dwell period, the air jet is switched off and the cuvette belt is advanced to bring the next cuvette into stationary position beneath

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the nozzle when the mixing process is repeated.

The mixing apparatus 15a, which is arranged after the further reagent dispenser 54, is identical to the apparatus 15 but the nozzle can be inclined at a 5 slightly shallower (more horizontal) angle since the liquid level will be slightly greater due to the addition of further reagent.

In the embodiment described above, the air-jet nozzle 150 is non-invasive of the cuvette, thus 10 maximizing throughput. However, in a modification as shown in Figure 11, the nozzle is inserted into the cuvette during mixing. This has the effect of limiting throughput and may result in contamination of the nozzle which can be dealt with by flushing the nozzle 15 with diluent between mixing operations. However, it does produce a system in which the angle of inclination 20 of the nozzle is not limited by the geometry of the cuvette so that it can be inclined more nearly to the horizontal thus desirably maximizing the horizontal component of the air jet. In this embodiment, the nozzle 150 has a dog-leg bend in it and it is mounted 25 on an elevator mechanism schematically represented at 160 by which it can be raised and lowered between a lowered, operative position as shown in solid outline and a raised, inoperative position as shown in dotted outline for cuvette indexing. With this arrangement the air jet angle can be reduced to as little as 8 degrees to the liquid surface (horizontal). An angle 30 of between about 8 degrees and about 15 degrees to the horizontal is preferred. As in the previous embodiment, the air jet is directed at the junction between the liquid surface and the cuvette wall.

The height of the nozzle above the liquid

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surface is to some extent determined by the angle of the air jet it produces, but when it is sufficiently close to the liquid surface that it becomes contaminated by splashing, it is cleaned between mixing 5 operations.

Although particular configurations and features of the present invention have been discussed in connection with the above-described preferred embodiments thereof, it should be understood that those 10 skilled in the art may make various changes, modifications and substitutions thereto without departing from the spirit and scope of the invention as defined in the appended claims.

For example, while in the embodiment shown in 15 Figures 6 to 8, the nozzle 150 is fixed in position during an operational sequence, it may be adjustable automatically to accommodate different liquid levels and/or cuvette sizes. Thus, its angle of inclination may be variable automatically within limits to 20 accommodate different liquid levels in response to a liquid level sensor.

Also, in the embodiment illustrated in Figures 6 to 8, the orifice of the air jet is arranged just above the wall of the cuvette diametrically 25 opposite where the air jet strikes the cuvette contents. It will be understood however that the orifice may be arranged out-of-line with the mouth of the cuvette as long as the air jet clears the wall of the cuvette at this point.

30 Although the nozzle 150 is shown aligned with the direction of advance of the cuvette belt, it will be understood that it may be oriented in other directions.

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While the systems described above are automated, it will be understood that in other systems a cuvette may be positioned manually beneath the nozzle or inserted over the nozzle.

5 It should be understood that the above described embodiments of the invention are illustrative only and that modifications thereof may occur to those skilled in the art. Accordingly, this invention is not to be regarded as limited to the embodiments disclosed
10 herein, but is to be limited only as defined by the appended claims.

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CLAIMS

1. A method of mixing materials, at least one of which is a liquid, in a cuvette, comprising the steps of introducing said materials into said cuvette then directing an air jet at an acute angle against the liquid surface in the cuvette adjacent its junction with the wall of the cuvette so as to agitate said materials sufficiently to cause said materials to mix.

2. A method according to Claim 1 including directing said air jet against the meniscus formed at the junction of the liquid surface and the wall of the cuvette.

3. A method according to Claim 1 including directing said air jet from a nozzle arranged outside the cuvette.

4. A method according to Claim 3 in which the air jet is inclined at an angle of between about 75 degrees and about 80 degrees to the liquid surface.

5. A method according to Claim 1 including the step of inserting a nozzle into the cuvette to a position above the liquid surface and directing said air jet against the liquid surface from said nozzle.

6. A method according to Claim 5 in which the air jet is inclined at an angle of between about 8 degrees and about 15 degrees to the liquid surface.

7. A method according to Claim 1 in which

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said air jet is applied for a period of about 3.5 to 4 about 4.5 seconds.

8. A method according to Claim 1 in which the cuvette is maintained stationary during said mixing.

9. A method of mixing liquid and particulate materials in a cuvette comprising the steps of dispensing at least one liquid material into the cuvette and dispensing at least one particulate material into the cuvette to partially fill the cuvette, and then positioning the cuvette beneath a nozzle and directing an air jet from said nozzle at an acute angle against the liquid surface in the cuvette adjacent its junction with the wall of the cuvette so as to form a vortex and produce a thorough mixing of said materials.

10. A method according to Claim 9 including directing said air jet against the meniscus formed at the junction of the liquid surface and the wall of the cuvette from a fixed nozzle arranged outside the cuvette while maintaining the cuvette stationary.

11. A method of analyzing a biological sample comprising the steps of dispensing a said sample into a cuvette with a reagent or a reagent and a diluent to partially fill the cuvette, then directing an air jet at an acute angle against the liquid surface in the cuvette adjacent its junction with the wall of the cuvette so as to create a vortex and produce a thorough mixing of said materials to facilitate

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reaction of the sample and analyzing the contents of the cuvette following said mixing.

12. A method according to Claim 11 in which said air jet is directed against the meniscus formed at the junction of said liquid surface and the wall of the cuvette.

13. A method according to Claim 11 including the step of aligning the cuvette with a fixed nozzle and directing said air jet into the cuvette from outside said cuvette while maintaining the cuvette stationary.

14. A method according to Claim 11 including the step of inserting a nozzle into the cuvette to a position above said liquid surface and directing said air jet against the liquid surface from said nozzle.

15. A method of analyzing liquid biological samples comprising the steps of dispensing a reagent into a cuvette with a diluent and mixing the contents of the cuvette to disperse the reagent in the diluent, adding a liquid biological sample so that the contents of the cuvette partially fill it and define a liquid surface bound by the wall of the cuvette, then directing an air jet at an acute angle against the liquid surface so as to agitate the contents and cause mixing thereof to facilitate reaction of the sample, and analyzing the contents of the cuvette following said mixing.

16. A method according to Claim 15 in which

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the air jet is directed at the liquid surface adjacent its junction with the wall of the cuvette.

17. A method of analyzing liquid biological samples, comprising the steps of:

dispensing a diluent and a reagent into a cuvette and mixing the contents of the cuvette;

adding a liquid biological sample, the contents of the cuvette partially filling the cuvette and defining a liquid surface bound by the wall of the cuvette;

directing an air jet at an acute angle against the liquid surface adjacent its junction with the wall of the cuvette so as to create a vortex and produce a thorough mixing of the contents to facilitate reaction of the sample; and analyzing the contents following said mixing.

18. A method according to Claim 17 in which said reagent is a dry particulate reagent and the reagent and diluent are mixed after dispensing.

19. A method according to Claim 17 in which the contents following said mixing are analyzed a plurality of times at intervals.

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20. A method according to Claim 19 including the step of dispensing after one analysis and prior to the next analysis, a further reagent into the cuvette and further mixing the contents of the cuvette by directing an air jet at an acute angle against the liquid surface in the cuvette adjacent its junction with the wall of the cuvette so as to create a vortex and produce a thorough mixing of the contents prior to said next analysis.

21. A method according to Claim 17 in which said analysis is by photometry.

22. A method according to Claim 17 including dispensing a second, liquid reagent into said cuvette prior to said mixing step (c).

23. A method according to Claim 17 in which said air jet is directed against the meniscus formed at the junction of the liquid surface and the wall of the cuvette.

24. A method according to Claim 17 including advancing the cuvette beneath a fixed nozzle and maintaining said cuvette stationary while directing said air jet against said liquid surface from outside the cuvette.

25. A method according to Claim 24 in which the liquid level in the cuvette is chosen so as to permit the air jet to be inclined at an angle of between about 75 degrees and about 80 degrees to the liquid surface.

26. A method according to Claim 17 including advancing the cuvette into alignment beneath a nozzle, lowering the nozzle into the cuvette closely above the liquid surface and maintaining the cuvette stationary while directing said air jet against said liquid surface from said nozzle.

27. A method according to Claim 26 in which the air jet is inclined at an angle of about 8 degrees to about 15 degrees to the liquid surface.

28. Apparatus for mixing materials, at least one of which is a liquid, including means for dispensing said materials into a cuvette, nozzle means for directing an air jet at an acute angle against the liquid surface so formed in the cuvette adjacent its junction with the wall of the cuvette so as to agitate said materials sufficiently to cause mixing of said materials, and means for advancing said cuvette from said dispensing means to align it with said nozzle means.

29. Apparatus according to Claim 28 in which said cuvette is partially filled by said dispensing means to a predetermined level and said cuvette is so aligned with said nozzle that said air jet is directed against the meniscus formed at the junction of the liquid surface and the wall of the cuvette.

30. Apparatus for mixing liquid and particulate materials in a cuvette, comprising:

means for dispensing at least one liquid and at least one particulate material into the cuvette to form a liquid surface in the cuvette bound by the wall of the cuvette at a predetermined level in the cuvette;

a fixed air jet nozzle;

means for advancing the cuvette from the dispensing means into stationary position beneath said air jet nozzle in alignment with said nozzle, said nozzle being so inclined as to direct an air jet at an acute angle against said liquid surface in the cuvette adjacent its junction with the wall of the cuvette so as to create a vortex such that the contents of the cuvette are raised above said liquid level against the cuvette wall behind said air jet and produce a thorough mixing of said materials.

31. Apparatus according to Claim 32 in which the nozzle is inclined at an angle of about 75 degrees to about 80 degrees to the horizontal.

32. Apparatus for mixing liquid and particulate materials in a cuvette comprising:

means for dispensing at least one liquid and at least one particulate material

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into the cuvette to partially fill the cuvette and form a liquid surface in the cuvette bound by the wall of the cuvette;

an air jet nozzle;

means for advancing the cuvette from the dispensing means into stationary position beneath said air jet nozzle; and

means for lowering said air jet nozzle into the cuvette to position it a predetermined height above said liquid surface in the cuvette, said nozzle being so inclined as to direct an air jet at an acute angle against said liquid surface in the cuvette adjacent its junction with the wall of the cuvette so as to create a vortex and produce a thorough mixing of said materials, and for raising said air jet nozzle out of said cuvette following said mixing.

33. Apparatus according to Claim 32 in which said nozzle is arranged to direct said air jet against the meniscus formed at the junction of the liquid surface and the wall of the cuvette.

34. A system for analyzing liquid biological samples comprising the following means and means for

advancing a cuvette between said means in order:

- (a) means for dispensing a reagent and a diluent into the cuvette and for mixing the reagent and the diluent to dispense the reagent in the diluent;
- (b) means for adding a liquid biological sample to the cuvette, the quantities of said reagent, diluent and sample dispensed being controlled so that together they partially fill the cuvette and define a liquid surface bound by the wall of the cuvette;
- (c) nozzle means for directing an air jet at an acute angle against the liquid surface so as to agitate the contents of the cuvette and cause mixing thereof to facilitate reactions of the sample; and
- (d) means for analyzing the reaction of the reagent with the sample following said mixing.

35. A system for analyzing liquid biological samples comprising the following means and means for advancing a cuvette between said means in order:

- (a) means for dispensing a reagent and a diluent into the cuvette and for mixing the reagent and diluent in the cuvette to dispense the reagent in the diluent;

- (b) means for adding a biological sample to the cuvette, the quantities of materials introduced into the cuvette being controlled so that together they partially fill the cuvette to a predetermined level and define a liquid surface bound by the wall of the cuvette;
- (c) an air jet nozzle, said advancing means being adapted to position the cuvette stationarily in predetermined alignment with said nozzle, said nozzle being adapted to direct our air jet against said liquid surface in the cuvette adjacent its junction with the wall of the cuvette so as to form a vortex and produce a thorough mixing of said materials; and
- (d) means for analyzing the light absorption of the cuvette following said mixing.

36. A system according to Claim 35 including said means:

- (a) includes means for dispensing a dry particulate reagent and a diluent into the cuvette, and means arranged following said dispensing means for mixing the reagent and diluent in the cuvette.

37. A system according to Claim 35 in which said air jet nozzle is fixed in position vertically and so inclined as to direct said air jet at said predetermined level of liquid adjacent said junction of its surface with the wall of the cuvette.

38. A system according to Claim 37 in which said air jet nozzle is inclined at between about 75 degrees and about 80 degrees to the horizontal.

39. A system according to Claim 36 in which means are provided for moving said nozzle into and out of a cuvette aligned therewith for operatively locating it in predetermined position above the liquid surface.

40. A system according to Claim 39 in which said air jet nozzle is inclined at between about 8 degrees and about 15 degrees to the horizontal.

41. A system according to Claim 37 in which said air jet nozzle is so arranged as to direct said air jet against the meniscus formed at the junction between said liquid surface and the wall of the cuvette.

42. A system according to Claim 37 in which said cuvette has a cross-section with unequal axes and the air jet is directed along the longer of said axes.

43. A system according to Claim 37 in which said analyzing means comprises a plurality of analyzing stations to which the cuvette is advanced in turn at

predetermined time intervals to monitor the reaction.

44. A system according to Claim 36 in which said dispensing means includes separate dispensers for said reagent and diluent and in which means is provided for dispensing a second, liquid reagent into said cuvette between said dispensers and said reagent and diluent mixing means.

45. A system according to Claim 43 including further dispensing means arranged between two successive said analyzing stations for dispensing a further reagent into the cuvette and further means arranged between said further dispensing means and the second of said two analyzing stations, comprising a nozzle adapted to direct an air jet at an acute angle against the liquid surface in a cuvette presented thereto adjacent its junction with the wall of the cuvette so as to create a vortex and produce a thorough mixing of the contents of the cuvette to facilitate further reaction of said sample.

46. A system according to Claim 37 in which said advancing means is adapted to advance a series of said cuvettes past said means in turn and in which means are provided for controlling said dispensing means to dispense different permutations of reagent, and samples into different cuvettes.

47. A system for analyzing liquid biological samples, comprising:

means for dispensing a reagent or a

reagent and a diluent, and a biological sample into a cuvette so that together they partially fill the cuvette to a predetermined level and define a liquid surface bound by the wall of the cuvette;

an air jet nozzle;

means for advancing the cuvette from said dispensing means into stationary position beneath said air jet nozzle in predetermined alignment with said nozzle, said nozzle being adapted to direct an air jet at an acute angle against said liquid surface in the cuvette adjacent its junction with the wall of the cuvette so as to form a vortex and produce a thorough mixing of said materials; and

means for analyzing the contents of the cuvette following said mixing.

48. A method of analyzing a biological sample comprising the steps of dispensing a said sample material into a cuvette with a reagent material or a reagent material and a diluent material to partially fill the cuvette, then thoroughly mixing said materials to facilitate reaction of the sample and analyzing the contents of the cuvette following said mixing.

49. A method of analyzing liquid biological

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samples, comprising the steps of:

dispensing a diluent and a reagent into a cuvette and mixing the contents of the cuvette; and

adding a liquid biological sample, the contents of the cuvette partially filling the cuvette and defining a liquid surface bound by the wall of the cuvette.

50. A system for analyzing liquid biological samples comprising the following means and means for advancing a cuvette between said means in order:

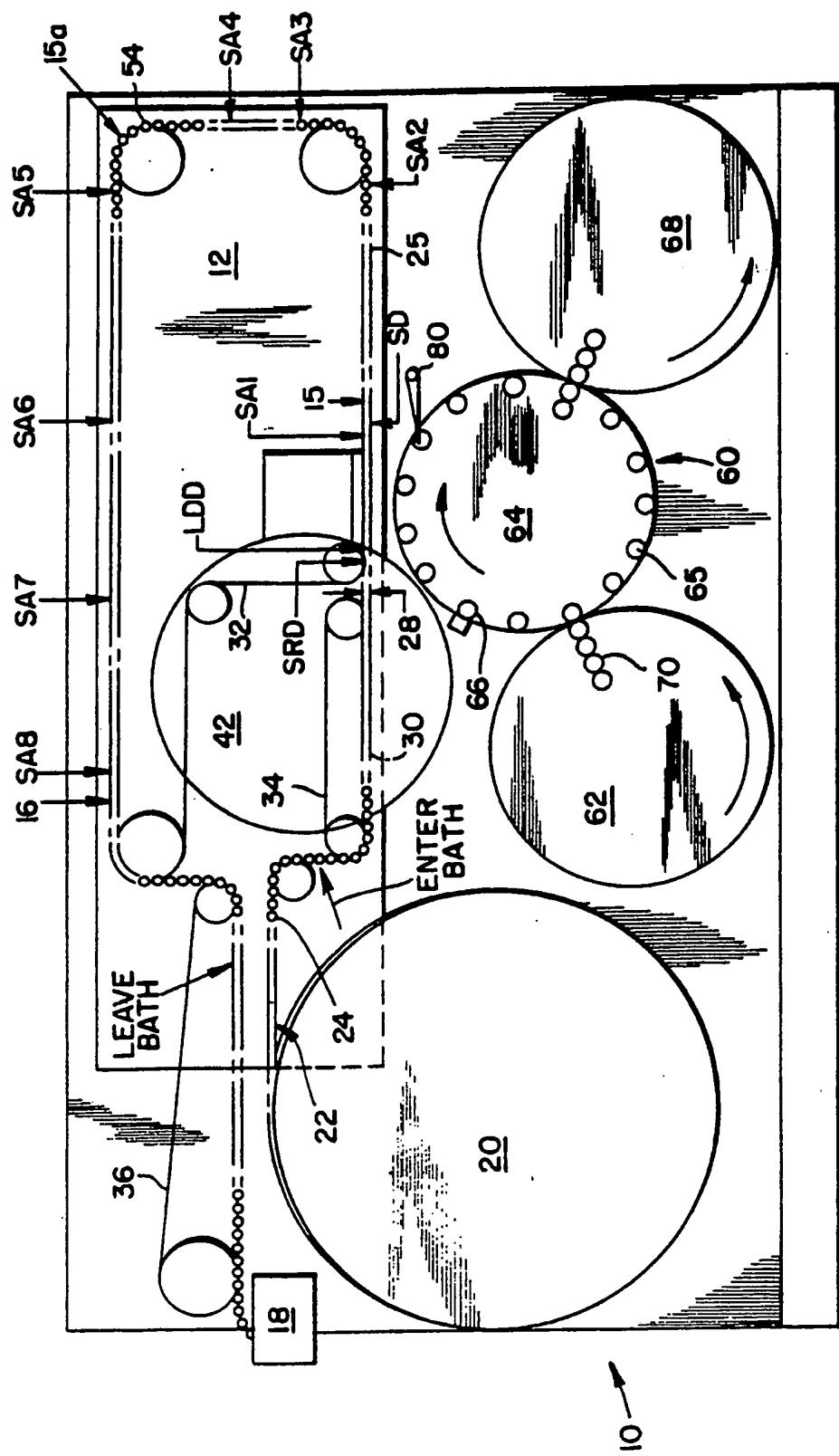
- (a) means for dispensing a reagent material and a diluent material into the cuvette and first means for mixing the reagent and diluent in the cuvette to disperse the reagent in the diluent;
- (b) means for adding a biological sample material to the cuvette, the quantities of materials introduced into the cuvette being controlled so that together they partially fill the cuvette;
- (c) second means for mixing the materials after said biological sample is added to the cuvette, said advancing means being adapted to position the cuvette stationarily in predetermined alignment

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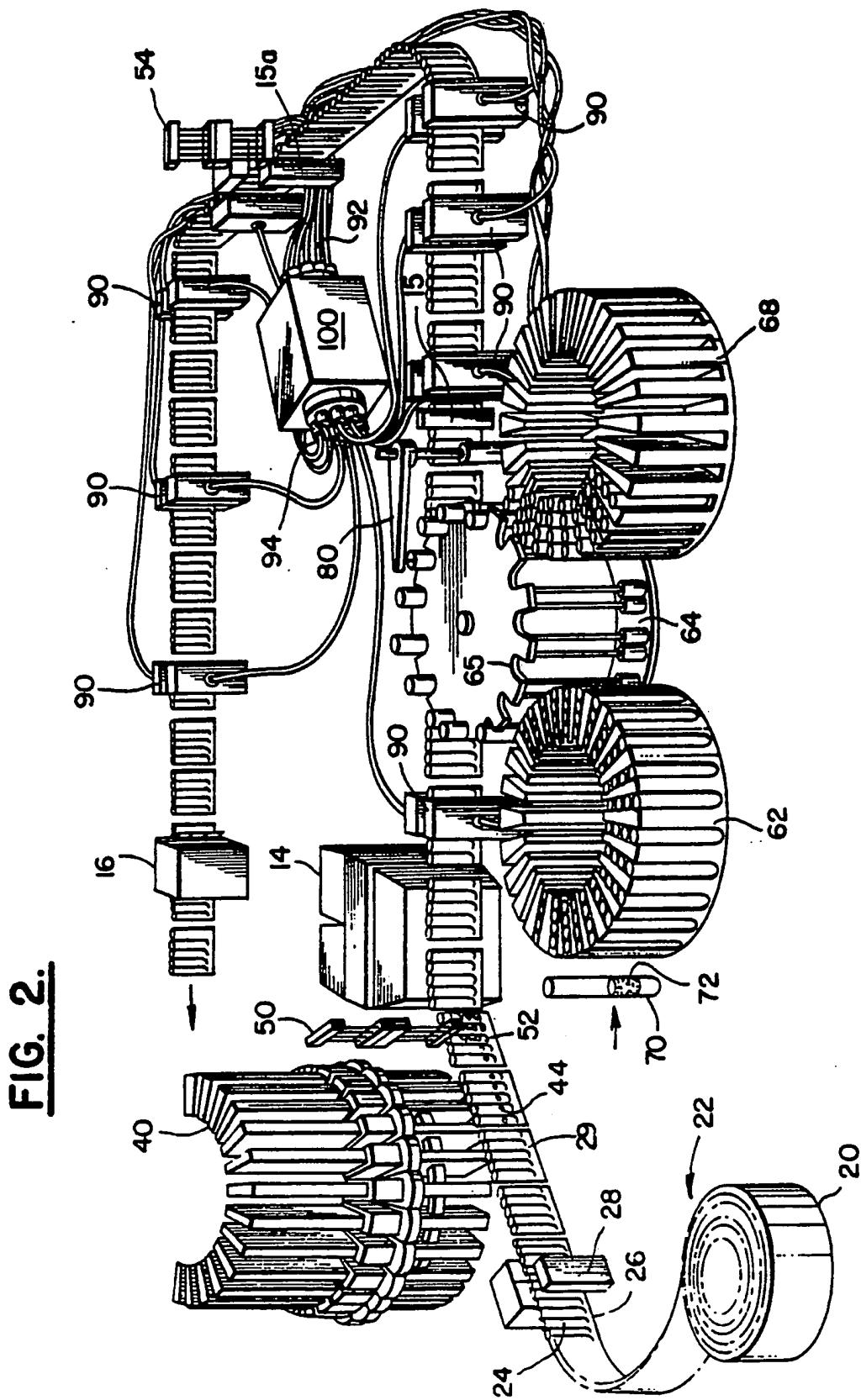
with said second mixing means; and

- (d) means for analyzing the light absorption of the cuvette following said second mixing.

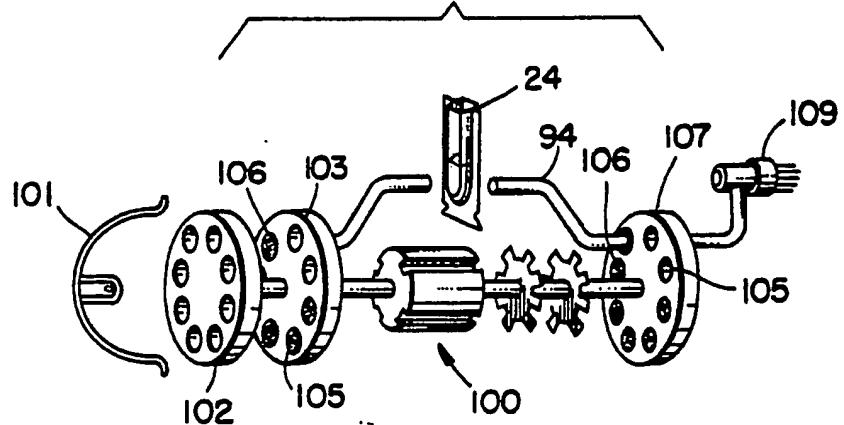
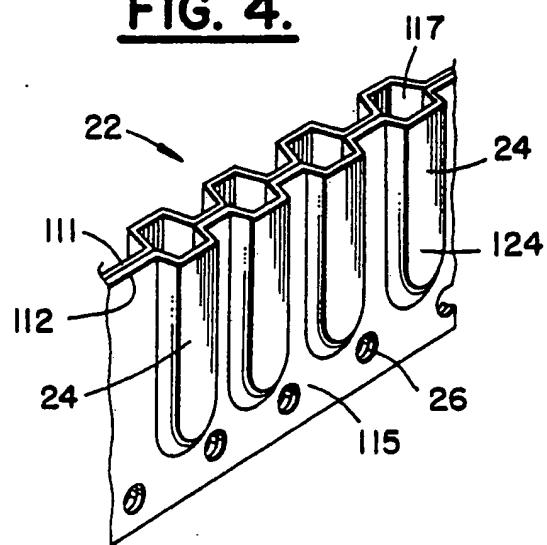
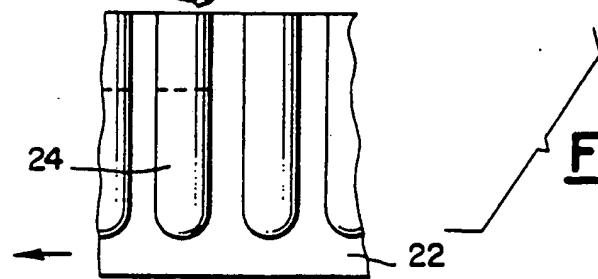
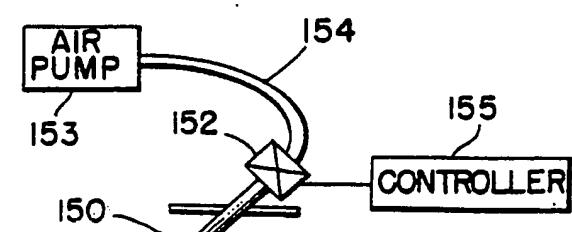
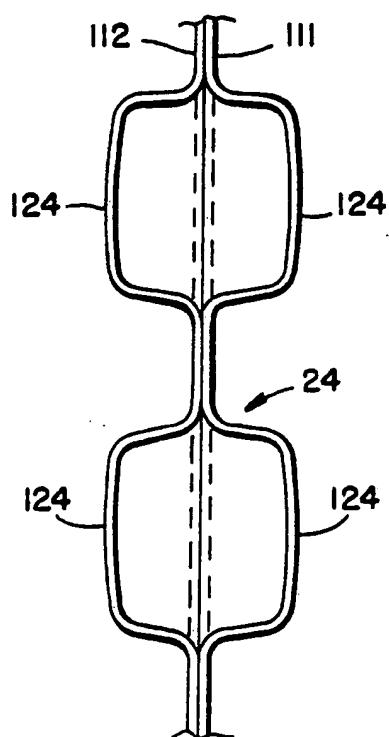
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FIG. 1.

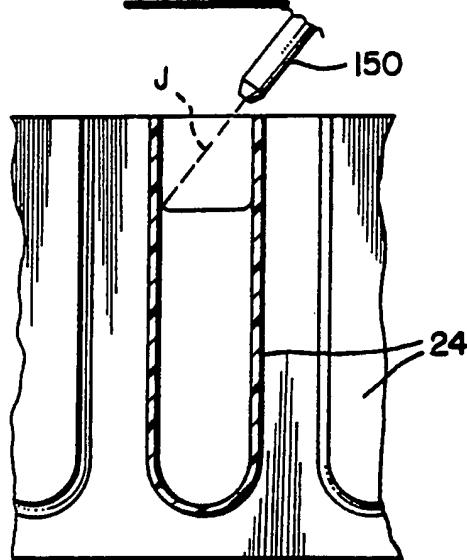
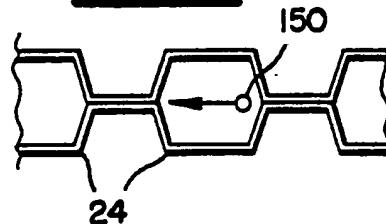
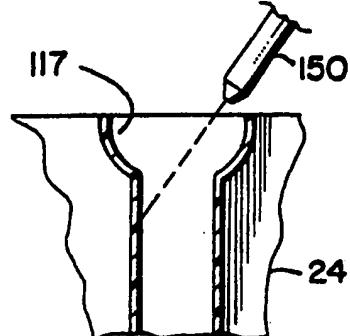
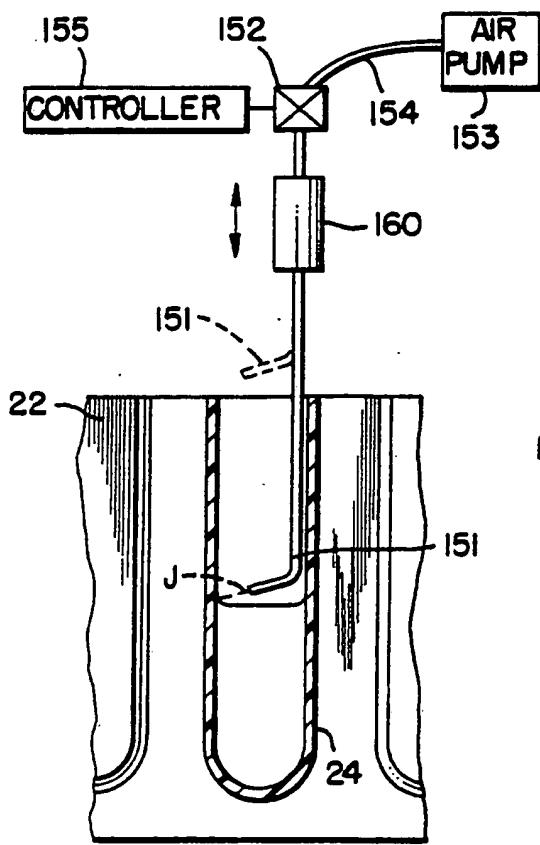
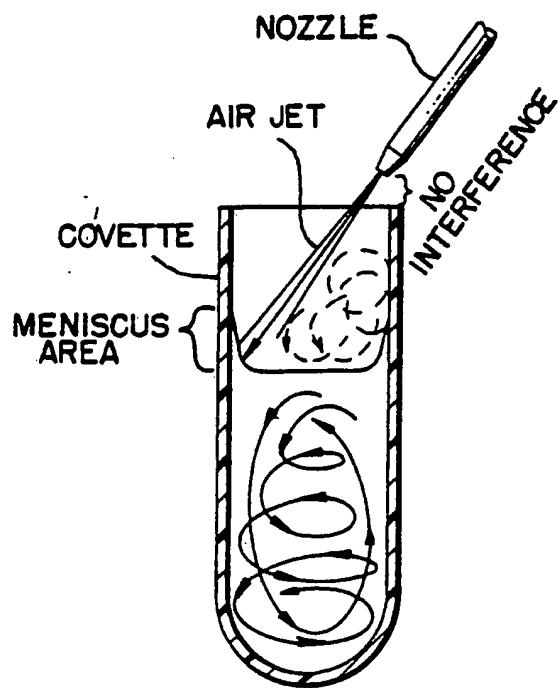
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FIG. 3.FIG. 4.FIG. 5.FIG. 6.

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FIG. 7.FIG. 8.FIG. 9.FIG. II.FIG. 10.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US85/00065

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC 84
G01N 1/00 G01N 35/04
G01N 35/02

II. FIELDS SEARCHED

Minimum Documentation Searched

Classification System	Classification Symbols
US	366/ 101, 106, 107, 127, 208, 218 436/ 47, 164, 177, 179 422/ 63, 64, 65, 66, 67, 99

**Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched 5**

III. DOCUMENTS CONSIDERED TO BE RELEVANT¹⁴

Category *	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
X	US. A, 3,398,935 PUBLISHED 27 AUGUST 1968,	1, 2, 5, 8, 10
	LIVESEY ET AL	12, 14
Y	US.A, 3,398,935 PUBLISHED 27 AUGUST 1968,	3, 4, 6, 7, 8-
	LIVESEY ET AL	10, 13, 15-47
X	US.A, 4, 325,910 PUBLISHED 20 APRIL 1982,	48, 49
	JORDAN	
Y	US.A, 4,325,910 PUBLISHED 20 APRIL 1982	30-47, 50
	JORDAN	
Y	N, THIS IS PARAMAX, THE PARAMAX ANALYTICAL	30-49
	SYSTEM, AMERICAN DADE; COPYRIGHT 1981	
X	US.A, 4,276,051 PUBLISHED 30 JUNE 1981,	48
	GINSBERG ET AL	
Y	US.A, 4,276,051, PUBLISHED 30 JUNE 1981,	49-50
	GINSBERG ET AL	

- **Special categories of cited documents:** 15
 - "A" document defining the general state of the art which is not considered to be of particular relevance
 - "E" earlier document but published on or after the international filing date
 - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 - "O" document referring to an oral disclosure, use, exhibition or other means
 - "P" document published prior to the International filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

IV. CERTIFICATION

IV. CERTIFICATION Date of the Actual Completion of the International Search ¹ 07 MARCH 1985	Date of Mailing of this International Search Report ² 05 APR 1985
International Searching Authority ¹ ISA/US	Signature of Authorized Office ³ MICHAEL S. MARCUS

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹⁰

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers _____, because they relate to subject matter ¹¹ not required to be searched by this Authority, namely:

2. Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out ¹², specifically:

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ¹³

This International Searching Authority found multiple inventions in this international application as follows:

CLAIMS 1-47 DRAWN TO A METHOD OF ANALYSIS INVOLVING AIR JET MIXING.

CLAIMS 48-50 A METHOD OF ANALYSIS INVOLVING MIXING PER SE.

1. As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the international application.

2. As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

The additional search fees were accompanied by applicant's protest.

No protest accompanied the payment of additional search fees.